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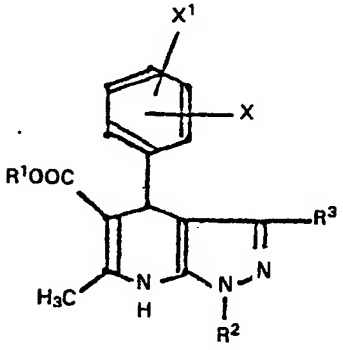
(54) Dihydropyrazolo(3,4-b)pyridine derivatives and production thereof.

(57) Dihydropyrazolo[3,4-b]pyridine derivatives represented by the general formula:



wherein X and X^1 each is hydrogen, nitro, or halogen which may be located at the position or positions 2, 3, and/or 6;
R^1 is alkyl;
R^2 is hydrogen, alkyl, cycloalkyl, or phenyl;
R^3 is hydrogen, straight or branched chain alkyl, or cycloalkyl which may be substituted by alkyl, substituted or unsubstituted phenyl, aralkyl, alkoxycarbonyl, or 5- or 6- membered heterocyclic group containing an oxygen or nitrogen, having calcium-antagonistic action are useful in treatment of diseases in the circulatory system such as angina pectoris, hypertension, cerebrovascular dysfunction, arrhythmia, and so on with no adverse reaction like negative inotropic action; prepared by the Michael addition and concurrent cyclization reaction of 2-acetyl cinnamic acid derivatives with 5-aminopyrazole derivatives.

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Dihydropyrazolo(3,4-b)pyridine Derivatives and Production thereof

The present invention relates to dihydropyrazolo-[3,4-b]pyridine derivatives having calcium antagonistic activity comparable to those of the known 1,4-dihydro-pyridine derivatives such as nifedipine, nisoldipine, nicardipine, and so on. Moreover, the derivatives have slight negative inotropic effect as adverse effect which is a problem in the prior art.

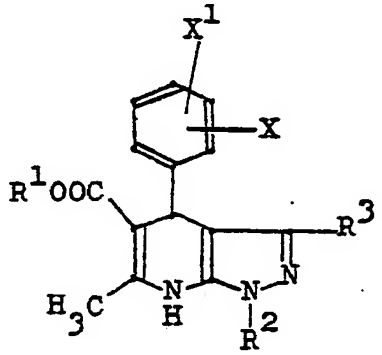
The compounds having calcium-antagonistic action have been utilized in treatment of diseases in the circulatory system such as angina pectoris, hypertension, cerebrovascular dysfunction, arrhythmia, and so on, and their high therapeutic efficacy has been appreciated. Especially, a series of compounds named 1,4-dihydro-pyridine derivatives have been investigated as calcium-antagonists. As the known calcium-antagonists, for example, nifedipine (U.S. Patent No. 3,485,847), nisoldipine (Japanese Patent Publication No. 56-47185), 4-amino-1,4-dihydropyridine derivatives (Japanese Patent Publication No. 57-20306), 2-pyridyl-1,4-dihydropyridine derivatives (Japanese Unexamined Patent Publication No. 54-48796)

are exemplified.

Meanwhile, the pyrazolodihydropyridine derivatives and their calcium-antagonistic action concerning the present invention have not yet been described in any literature.

The present invention relates to dihydropyrazolo-[3,4-b]pyridine derivatives , production thereof, and pharmaceutical compositions thereof;

1) Dihydropyrazolo[3,4-b]pyridine derivatives represented by the general formula (I):



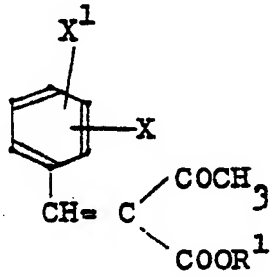
[wherein X and X^1 each is hydrogen, nitro, or halogen which may be located at the position or positions 2, 3, and/or 6;

R^1 is C_1- C_4 alkyl;

R^2 is hydrogen, C_1- C_4 alkyl, C_4- C_6 cycloalkyl, or phenyl;

R^3 is hydrogen, C_1- C_8 straight or branched chain alkyl, or C_3- C_7 cycloalkyl which may be substituted by C_1- C_3 alkyl, substitued or unsubstituted phenyl, C_7- C_9 aralkyl, C_1- C_4 alkyloxycarbonyl, or 5- or 6- membered heterocyclic group containing an oxygen or nitrogen];

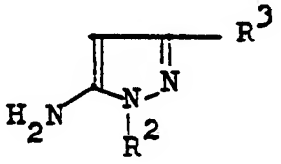
2) A process which comprises reacting a compound represented by the general formula (II):



(II)

[wherein X , X^1, and R^1 each has the same significance as defined above]

with a compound represented by the general formula (III):



(III)

[wherein R^2 and R^3 each has the same significance as defined above]

to yield the dihydropyrazolo[3,4-b]pyridine derivatives represented by the general formula (I).

3) Medicinal compositions comprising one or more members selected from the group consisting of dihydropyrazolo-[3,4-b]pyridine derivatives represented by the general

formula (I) and their pharmaceutical acceptable acid addition salts and pharmaceutical carriers.

The compounds (I) of the present invention are classified into calcium-antagonists having potent antihypertensive action and coronary vasodilating action and useful in treatment of diseases in the circulatory system such as angina pectoris, hypertension, cerebrovascular dysfunction, arrhythmia, and so on. The compounds (I) have slight negative inotropic effect with weak acute toxicities in mice.

The compounds (I) of the present invention are prepared by the Michael addition and concurrent cyclization reaction of heterocyclic groups with α,β-unsaturated ketones; the process for production thereof is also new in respect of providing new aromatic condensed dihydropyridines.

In the brief summary of the invention, definition relating to the general formulas (I) - (III);
the halogen means fluorine, chlorine, bromine, and iodine, particularly, chlorine is preferred;
the C_1- C_4 alkyl means straight or branched chain lower alkyls; for example, methyl, ethyl, i-propyl, t-butyl, and

the like;

the C_4- C_6 cycloalkyl includes cyclobutyl, cyclopentyl, cyclohexyl, and the like;

the C_1- C_8 straight or branched chain alkyl includes methyl, ethyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, 3-methylpent-3-yl, n-hexyl, n-heptyl, n-octyl, and the like;

the C_3- C_7 cycloalkyl which may be substituted by C_1- C_3 alkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 4-methylcyclohexyl, 1-ethylcyclohexyl, and the like;

in the substituted or unsubstituted phenyl group the substituent includes, for example, chlorine, trifluoromethyl, cyano, methoxy, methoxycarbonyl, ethoxycarbonyl, and the like;

definitely such phenyl includes phenyl, 3-chlorophenyl, 3,5-dichlorophenyl, 3-trifluoromethylphenyl, 3-cyanophenyl, 4-methoxyphenyl, 3-methoxycarbonylphenyl, 3-ethoxycarbonylphenyl, and the like;

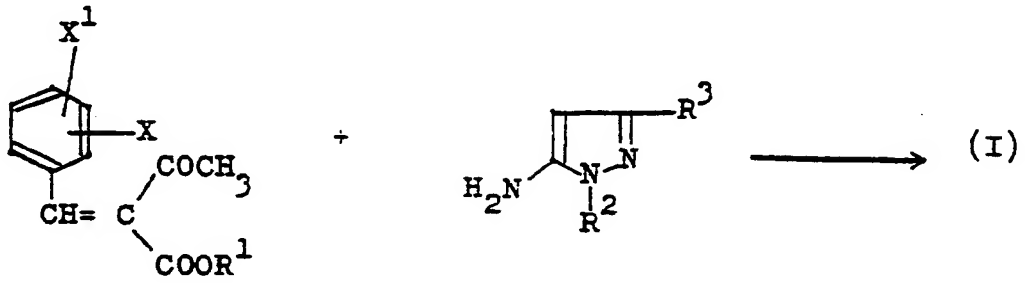
the C_7- C_9 aralkyl,includes benzyl, phenethyl, phenylpropyl, tolylmethyl, and the like;

the C_1- C_4 alkyloxycarbonyl includes methoxycarbonyl, ethoxycarbonyl, i-propoxycarbonyl, t-butoxycarbonyl, and the like;

the 5- or 6- membered heterocyclic group containing an oxygen or nitrogen includes α-pyridyl, β-furyl, 1-methylimidazol-2-yl, and the like;

The objective compounds of the present invention

(I) can be prepared easily by the reaction of α,β-unsaturated ketone reagents (II) with 5-aminopyrazole compounds (III) as shown in the following reaction sequence.



(II) (III) (I)

[wherein X, X^1, R^1, R^2, and R^3 each has the same significance as defined above].

The above reaction is conducted in the absence or presence of solvents.

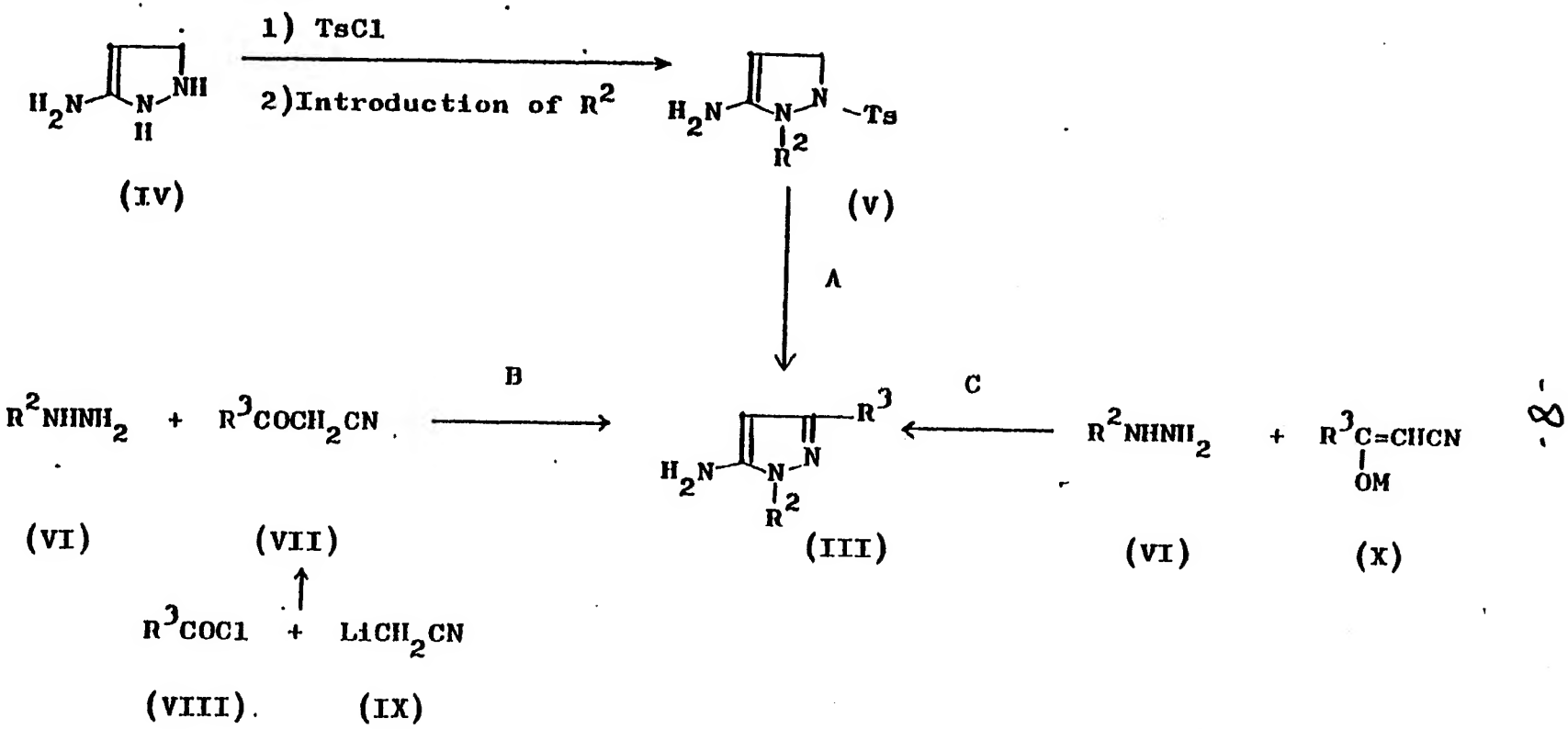
As the solvent used in the reaction, alcoholic solvents including methanol, ethanol, i-propanol, t-butanol, ethylene glycol, and the like;
hydrocarbon solvents including benzene, toluene, xylene, and the like;
ether solvents including ether, tetrahydrofuran, dioxan, glyme, diglyme, and the like;
halogenohydrocarbons including methylene chloride, chloroform, dichloroethane, carbon tetrachloride, and the like;
ester solvents including ethyl acetate, and the like;
and acetic acid, dimethylformamide, and the like may be

exemplified. If necessary, an acid or inorganic base may be used as catalyst. As the acid catalyst, inorganic acids such as sulfuric acid, hydrochloric acid, phosphoric acid, and the like;
organic acids such as p-toluenesulfonic acid, acetic acid, formic acid, and the like;
and Lewis acid such as boron trifluoride, zinc chloride, aluminum chloride, magnesium chloride, tin chloride, and the like may be exemplified. As the organic base catalyst, triethylamine, pyridine, pyrrolidine, piperidine, and the like may be exemplified. The reaction is conducted at room temperature or under heating (20 - 100 °C), and usually terminates within a period of several hours to several days.

The starting 5-aminopyrazole compounds and α,β-unsaturated ketone reagents used in the reaction are prepared in the manner as shown below.

(1) Preparation of 5-aminopyrazole compounds (III)

The 5-aminopyrazole compounds (III) can be prepared accroding to three processes as shown in the following reaction sequence.

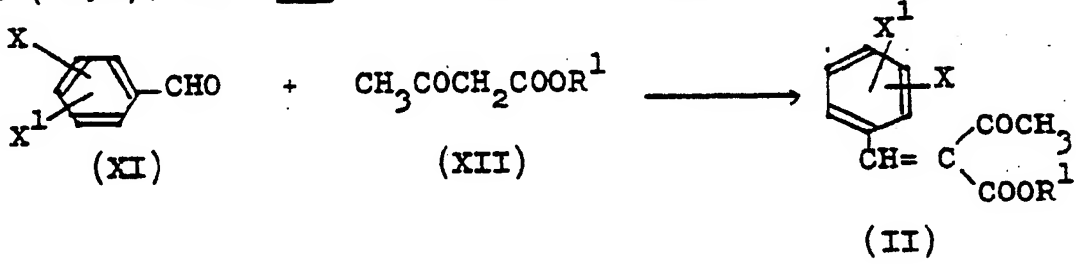


[In the above sequence, R^2 and R^3 each has the same significance as defined above and M represents alkali metal.]

In the above reaction sequence the 5-aminopyrazole compounds (III) when R^3 is hydrogen may be prepared according to the process A from the compounds (IV) by tosylation and introduction of R^2 followed by elimination of the tosyl group with a base [Chem. Ber. 98 3368 (1965)]. The compounds (III) when R^3 is neither hydrogen nor alkoxycarbonyl may be prepared according to the process B by cyclization reaction of hydrazine or methyl- or phenylhydrazines (VI) with a member of β-ketonitriles (VII). The β-ketonitriles (VII) are prepared by reaction of a member of acid chlorides (VIII) with the lithium acetonitrile (IX). The compounds (III) when R^3 is alkoxycarbonyl are prepared by cyclization reaction of a member of hydrazines (VI) with the alkali metal salt of alkyl 3-cyanopyruvates (X).

(2) Preparation of α,β-unsaturated ketone reagents (II)

The α,β-unsaturated ketone reagents (II) are prepared by the condensation of the aldehydes (XI) with the acetoacetic esters (XII) according to the following reaction sequence [J. Chem. Soc., 81 1212 (1902), Chem. Ber. 29 172 (1896), Ann. 218 170 (1883), J. Chem. Soc., 3092 (1962)].



(XI) (XII) (II)

[wherein X, X^1, and R^1 each has the same significance as defined above].

The compounds of the present invention prepared from the 5-aminopyrazole compounds (III) by the reaction with the α,β-unsaturated ketone reagents (II) as mentioned above are exemplified as follows.

Ethyl 3-cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine -5-carboxylate,

Ethyl 1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo-[3,4-b]pyridine-5-carboxylate,

Methyl 1,6-dimethyl-4-(2-nitrophenyl)-4,7-dihydropyrazolo-[3,4-b]pyridine-5-carboxylate,

Methyl 3-isopropyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-(n-butyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-cyclobutyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-cyclopentyl-1,6-dimethyl-4-(2-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Isopropyl 3-cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 3-cyclopentyl-1,6-dimethyl-4-(2-chlorophenyl)-

4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 3-cyclopentyl-1,6-dimethyl-4-(2,6-dichlorophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-cyclohexyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-benzyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 3-phenyl-6-methyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 1,3-diphenyl-6-methyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-phenyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 3-phenyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-phenyl-1,6-dimethyl-4-(2-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 3-(3-chlorophenyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-(3,5-dichlorophenyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 3-(3,5-dichlorophenyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 3-(3-trifluoromethylphenyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-

carboxylate,

Ethyl 3-(3-cyanophenyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 3-(3-methoxycarbonylphenyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 3-(3-ethoxycarbonylphenyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 3-(α-pyridyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-(β-furyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-methoxycarbonyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 3-ethoxycarbonyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-isopropoxycarbonyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 3-(4-methoxyphenyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 1,3-dicyclopentyl-6-methyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-isobutyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-(t-butyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-(n-pentyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-(3-methylpent-3-yl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-cyclopropyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-cyclohexyl-1,6-dimethyl-4-(2-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-cycloheptyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-(4-methylcyclohexyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-(1-ethylcyclohexyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate,

Methyl 3-(1-methyl-imidazol-2-yl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate.

The compounds of the present invention have

potent antihypertensive action and coronary vasodilating action which are based on calcium-antagonistic action; they also have platelet aggregation action, but they are advantageous in having nc unpleasant systole inhibitory action undesired as pharmaceutical drug with lower toxicity. The biological tests of the compounds mentioned below were conducted as follows.

(The compounds)

(A): Nifedipine

(B): Methyl 3-cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate

(C): Ethyl 3-cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7- dihydropyrazolo[3,4-b]pyridine-5-carboxylate hydrochloride

(1) Antihypertensive action

(Experimental method)

Female Spontaneously Hypertensive Rats (hereinafter abbreviated to as SHR) in which systolic pressure was about 160 mmHg were used without anesthetization. After SHR were warmed at 50 °C for 2 - 3 minutes, systolic blood pressure was measured indirectly by the tail-cuff method using a Physiograph and Electrosphygmomanometer (DMP-4B and PE-300, Narco Biosystems, Inc., Houston). Each compound was intraperitoneally administered to SHR at a dose of 3 mg/kg body weight.

(Result)

Table 1

Compounds	Maximum Hypotension (mmHg)	Duration of Effect (hours)
(A)	45	6
(B)	66	16
(C)	42	14

(2) Coronary vasodilating action,

Negative inotropic action

(Experimental method)

The guinea-pigs (body weight: 400 - 800 g) of both sexes were hit on the head hard, and the arteria carotis was cut off and phlebotomized. The isolated heart was perfused at pressure of 50 cm H_2O according to the Langendorff method [Basic Pharmacology & Therapeutics, 9 (4), 181 (1981)]. Krebs-Ringer bicarbonate solution containing 0.5 % defibrinated blood at 27 °C was used as perfusate, into which a mixture of 95 % oxygen and 5 % carbon dioxide was introduced continuously. The perfusion flow was led into a drop counter, and its increase or decrease was regarded as an indication of coronary vasodilation or vasoconstriction;

the isometric contraction of apex was recorded along with

the drop number of coronary perfusate on a Recticorder (RJG 3006, Nihon Koden) by way of an F-D pick-up (SB-1T, Nihon Koden). Each compound was administered into a rubber tube connected with an arota cannula at a dose of 0.1 μg, 1 μg, and 10 μg.

(Result)

Table 2 Coronary vasodilating action

Compounds	Perfusion Flow Change (%)		
	0.1 μg	1 μg	10 μg
(A)	+ 38	+ 100	
(B)	+ 26	+ 73	+ 180
(C)	+ 40	+ 79	+ 93

Table 3 Negative inotropic action

Compounds	Change of Contractile Tension (%)		
	0.1 μg	1 μg	10 μg
(A)	- 15	- 57	
(B)	0	0	0
(C)	0	0	0

(3) Acute toxicity

(Experimental method)

In female DS mice (body weight: about 20 g), LD_{50} value after the intravenous administration of the compounds was calculated by the Brownlee's up and down method [J. Am. Sat. As., 48 262 (1953)].

(Result)

Table 4

Compounds	LD_{50} mg/Kg
(A)	10.7
(B)	31.5
(C)	50.6

In consideration of the results mentioned above, the compounds of the present invention have remarkably potent antihypertensive and coronary vasodilating actions but slight negative inotropic action with lower acute toxicity, and so they can be utilized as drugs acting on the circulatory system with fewer adverse effects for men or animals.

The compounds of the present invention may be administered to men or animals orally or parenterally and formulated into various dosage forms according to

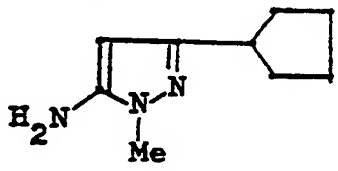
the administration method. For example, tablets, capsules, pills, granules, fine granules, aqueous solution, emulsion, and so on may be prepared. In the pharmaceutical preparation, usual conventional carriers or diluents, such as lactose, sucrose, starch, cellulose, talc, magnesium stearate, magnesium oxide, calcium sulfate, powdered gum arabic, gelatin, sodium arginate, sodium benzoate, stearic acid, and the like may be used. As injection, a solution in water for injection, saline solution, Ringer solution, and so on, or a suspension in sesame oil may be used.

The compounds of the present invention may be administered at a dose of about 1 - 50 mg a day for an adult in oral administration and at a dose of about 0.5 - 20 mg in intraveneous injection.

The present invention will be explained by the following Examples and Reference examples.

Example 1

Preparation of ethyl 3-cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate



1

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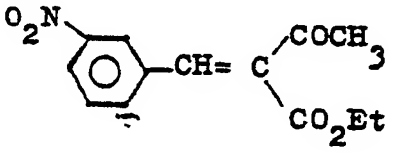

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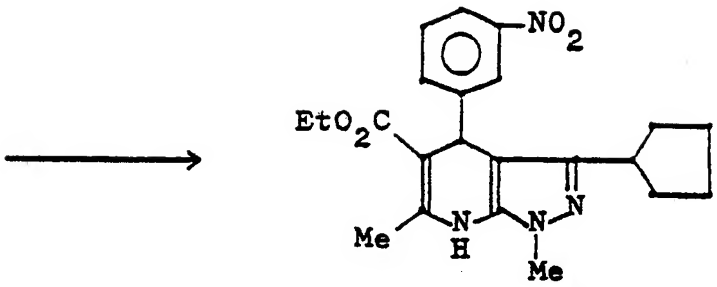


2

A mixture of 0.83 g (5 mmol) of 5-amino-3-cyclopentyl-1-methylpyrazole 1 and 1.32 g (5 mmol) of ethyl 3-nitrobenzylidene acetate 2 in 10 ml of t-butanol is heated at 80 °C under nitrogen gas for 3 days. The mixture is concentrated under reduced pressure, and the resulting residue is dissolved in chloroform, washed with an aqueous sodium bicarbonate solution and then with an a aqueous sodium chloride solution. The solution is dried with magnesium sulfate and chromatographed on a column of silica gel. The chloroform-ethyl acetate (20:1) fraction gives 2 g of the titled compound as an yellow oily material.

IR: ν_{max}^{Nujol} 3270, 3150, 1690, 1350 cm^{-1}

NMR: δ^{CDCl_3} 1.17 (3H, t), 1.00 - 2.80 (9H, m), 2.38, 3.67 (3H x 2, s), 4.03 (2H, q), 5.25 (1H, s), 7.13 - 8.10 (4H, m)

The titled compound (2 g) is converted into the hydrochloride on treatment with an ether-hydrochloric acid mixture, which is recrystallized from acetone to give

1.75 g of the hydrochloride. (Yield: 78.4 %)

m.p. 170 - 173 °C

Elemental analysis

Calcd (%): C, 59.12; H, 6.09; N, 12.54 (for $C_{22}H_{26}N_4O_4.HCl$)

Found (%): C, 58.90; H, 6.10; N, 12.57

IR: ν_{max}^{Nujol} 2630, 2550, 1680, 1347 cm^{-1}

NMR: δ^{CDCl_3} 0.93 - 2.90 (9H, m), 1.17 (3H, t), 2.61 (3H, s)
4.03 (2H, q), 6.03 (1H), 5.22 (1H, s), 7.23 - 8.17 (4H, m)

Examples 2 - 42

In the same manner as in Example 1, the compounds described in Table 5 can be prepared. Tables 6 and 7 show the data of each product, i.e. physical constants, elemental analysis, IR spectra, and NMR spectra.

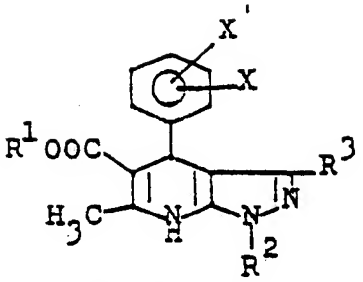
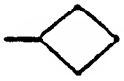
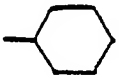
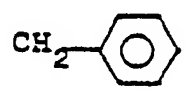
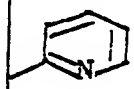
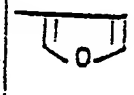
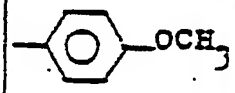
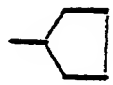
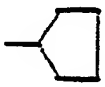
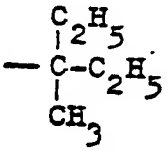
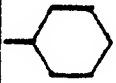
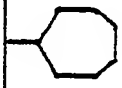
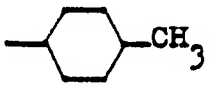
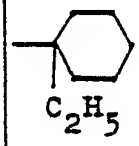
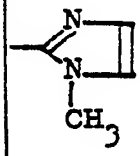


Table 5

Ex.	R′	R^2	R^3	X . X′	Yield (%)
2	C_2H_5	CH_3	H	3-NO_2,H	47.4
3	CH_3	"	"	2-NO_2,H	42.1
4	"	"	i-C_3H_8	3-NO_2,H	92.6*
5	"	"	n-C_4H_9	"	96.7
6	"	"		"	68.5
7	"	"		2-NO_2,H	77.6
8	"	"	"	3-NO_2,H	60.6
9	i-C_3H_8	"	"	"	68.2*
10	C_2H_5	"	"	2-Cl,H	59.0*
11	"	"	"	2,6-Cl_2	15.7
12	CH_3	"		3-NO_2,H	71.7*
13	"	"		"	71.4*

26	"	"		"	75.7
27	CH_3	"		"	77.7
28	"	"	$COOCH_3$	"	59.8
29	C_2H_5	"	$COOC_2H_5$	"	58.9
30	CH_3	"	$COO\text{-}i\text{-}C_3H_8$	"	56.5
31	C_2H_5	"		"	80.4
32	CH_3			"	71.8
33	"	CH_3	$i\text{-}C_4H_9$	"	59.0
34	"	"	$t\text{-}C_4H_9$	"	38.8
35	"	"	$n\text{-}C_5H_{11}$	"	85.7*
36	"	"		"	57.4*
37	"	"		"	73.7
38	"	"		2-NO_2,H	79.6
39	"	"		3-NO_2,H	95.2

40	"	"		"	53.2
41	"	"		"	59.6*
42	"	"		"	76.8

* Hydrochloride

Table 6

Ex.	Appearance	Solvent in Recrystallization	M.P. (°C)	Molecular Formula	Elemental Analysis					
					Calcd.			Found.		
					C	H	N	C	H	N
2	YP	Ethyl acetate	153-154	$C_{17}H_{18}N_4O_4$	59.64	5.30	16.37	59.68	5.25	16.33
3	"	Isopropanol	213-214	$C_{16}H_{16}N_4O_4$	58.53	4.91	17.07	58.68	4.89	17.14
4	"	Methanol	214-220	$C_{20}H_{24}N_4O_4 \cdot HCl$	57.21	5.76	13.34	56.93	5.97	13.36
5	OP	Ether	129-132	$C_{20}H_{24}N_4O_4$	62.48	6.29	14.58	62.52	6.31	14.46
6	YP	Ethyl acetate	183-185	$C_{20}H_{22}N_4O_4$	62.81	5.80	14.65	62.63	5.83	14.58
7	"	Ethanol	208-213	$C_{21}H_{24}N_4O_4$	63.62	6.10	14.13	63.50	6.15	14.10
8	"	Isopropyl ether	172-173	$C_{21}H_{24}N_4O_4$	63.62	6.10	14.13	63.42	6.08	14.07
9	CP	Isopropanol	170-190 (dec.)	$C_{23}H_{25}N_4O_4 \cdot HCl \cdot \frac{1}{2}H_2O$	59.29	5.84	12.03	59.72	6.31	12.03
10	"	Methanol-Acetone	160-170 (dec.)	$C_{22}H_{26}N_3O_2Cl \cdot HCl$	60.55	6.24	9.63	60.63	6.31	9.75
11	"	Isopropyl ether	146-148	$C_{22}H_{25}N_3O_2Cl_2 \cdot \frac{1}{2}H_2O$	59.60	5.91	9.47	59.56	6.04	9.41
12	YP	Methanol	195-230 (dec.)	$C_{22}H_{26}N_4O_4 \cdot HCl$	59.13	6.09	12.54	58.76	6.09	12.50
13	CP	Methylene chloride -Ether	124-126	$C_{23}H_{22}N_4O_4 \cdot HCl \cdot \frac{1}{2}H_2O$	59.54	5.22	12.07	59.35	5.36	11.83
14	YP	Benzene	233-234	$C_{22}H_{20}N_4O_4$	65.33	4.99	13.86	65.23	4.83	13.93
15	"	Ethyl acetate	214-215	$C_{28}H_{24}N_4O_6$	69.99	5.03	11.66	70.28	5.09	11.68
16	OP	〃	209-210	$C_{22}H_{20}N_4O_4$	65.33	4.99	13.86	65.42	4.91	13.89
17	YN	Methylene chloride -Ether	157-158	$C_{23}H_{22}N_4O_4$	66.01	5.30	13.39	65.94	5.16	13.33

18	OP	Chloroform	205-206	$C_{22}H_{20}N_4O_4 \cdot \frac{1}{2}H_2O$	63.91	5.12	13.55	64.17	5.06	13.64
19	YP	Ethanol	214-216	$C_{23}H_{21}N_4O_4Cl$	61.00	4.67	12.37	61.03	4.63	12.38
20	"	Tetrahydrofuran -Ethanol	263-264	$C_{22}H_{18}N_4O_4Cl_2$	55.82	3.83	11.84	55.80	3.82	11.74
21	"	Methylene chloride - Ether	222-224	$C_{23}H_{20}N_4O_4Cl_2$	56.68	4.14	11.50	56.32	4.22	11.43
22	"	Methanol	217-218	$C_{24}H_{21}N_4O_4F_3$	59 25	4.35	11.52	59.31	4.39	11.56
23	YN	"	211-214	$C_{24}H_{21}N_5O_4$	65 00	4.77	15.79	64.87	4.89	15.67
24	OP	Ethanol	182-183	$C_{25}H_{24}N_4O_6$	63.01	5.08	11.76	62.93	5.11	11.80
25	YN	Methanol	225-227	$C_{26}H_{26}N_4O_6$	63 66	5.34	11.42	63.42	5.36	11.39
26	YP	Isopropanol	213-214	$C_{22}H_{21}N_5O_4$	63.00	5.05	16.70	63.16	4.94	16.63
27	"	Ethanol	195-198	$C_{20}H_{18}N_4O_5$	60.91	4.60	14.21	60.85	4.70	14.08
28	"	Ethyl acetate	206-209	$C_{18}H_{18}N_4O_6$	55.95	4.70	14.50	55.91	4.71	14.40
29	YN	"	133-135	$C_{20}H_{22}N_4O_6$	57.96	5.35	13.52	57.29	5.34	12.97
30	YP	"	180-182	$C_{20}H_{22}N_4O_6$	57.96	5.35	13.52	57.73	5.36	13.30
31	"	"	159-161	$C_{24}H_{24}N_4O_5$	64 27	5.39	12.49	64.33	5.42	12.48
32	OP	Ethanol	175-177	$C_{25}H_{30}N_4O_4$	66.66	6.71	12.44	66.68	6.68	12.44

33	YP	Ethyl acetate	110-115	$C_{20}H_{24}N_4O_4$	62.48	6.29	14.58	62.12	6.12	14.76
34	〃	〃	153-154	$C_{20}H_{24}N_4O_4 \cdot \frac{1}{2}H_2O$	61.06	6.40	14.24	61.25	6.52	13.88
35	〃	Ethanol	140-155	$C_{21}H_{26}N_4O_4 \cdot HCl$	58.00	6.26	12.88	58.03	6.37	12.71
36	CP	Acetone	172-175	$C_{22}H_{28}N_4O_4 \cdot HCl$	58.86	6.51	12.48	58.59	6.47	12.46
37	YP	Ethyl ether	100-102	$C_{19}H_{20}N_4O_4$	61.94	5.47	15.21	61.84	5.56	15.05
38	〃	Methyl cyanide	215-219	$C_{22}H_{26}N_4O_4$	64.37	6.39	13.65	64.21	6.31	13.52
39	〃	Ethyl ether	199-200	$C_{23}H_{28}N_4O_4$	65.07	6.65	13.20	65.13	6.77	13.10
40	〃	Isopropanol	197-198	$C_{23}H_{28}N_4O_4$	65.07	6.65	13.20	65.09	6.60	13.05
41	PL	Ethanol	175-176	$C_{24}H_{30}N_4O_4 \cdot HCl$	60.69	6.58	11.80	60.35	6.43	11.77
42	YN	Methanol	207-208 (dec.)	$C_{20}H_{20}N_6O_4 \cdot CH_3OH$	57.00	5.92	19.00	57.10	5.48	19.05

* YP=Yellow prisms, CP=Colorless prisms, OP=Orange prisms, YN=Yellow needles, PL=Colorless plates

Table 7

Ex.	I R ($\nu_{max}^{cm^{-1}}$) NH	CO	NO_2	N M R (δ^{CDCl_3})
2	3340	1690	1343	1.10(3H,t), 2.45(3H,s), 3.70(3H,s), 4.00(2H,q), 5.30(1H,s), 7.00(1H,s), 7.20(1H,bs), 7.30-8.10(4H,m)
3	3280 3175	1680	1350	2.45(3H,s), 3.40(3H,s), 3.70(3H,s), 5.70(1H,s), 6.80(1H,bs), 7.30-7.85(4H,m)
4	3430 3290	1690	1350	0.90(3H,d), 1.10(3H,d),1.20(3H,t), 2.40(3H,s), 2.20-2.80(1H,m), 3.70(3H,s), 4.05(2H,m), 5.30(1H,s), 6.90(1H,bs), 7.35-8.10(4H,m)
5	3350	1693	1345	0.53-1.53(7H,m), 2.20(2H,m), 2.40(3H,t), 3.59(3H,s), 3.68(3H,s), 5.25(1H,s), 7.44(1H,bs), 7.23-8.13(4H,m)
6	3375	1705	1350	2.10-3.07(7H,m), 2.37(3H,s), 3.56(3H,t), 3.65(3H,s), 5.16(1H,s), 7.37-7.90(5H,m)
7	3290	1673	1353	0.87-3.10(9H,m), 2.32(3H,s), 3.32(3H,s), 3.67(3H,s), 5.62(1H,s), 7.10-7.83(4H,m)
8	3375	1700	1380	1.17-2.83(9H,m), 2.27(3H,s), 3.58(3H,s), 3.67(3H,s), 5.25(1H,s), 6.70(1H,bs), 7.27-8.10(4H,m)
9	2560	1693	1353	*1.03(3H,d), 1.25(3H,d), 1.53-2.60(9H,m), 2.38(3H,s), 3.65(3H,s), 4.90(2H,q), 5.23(1H,s), 7.40-7.93(5H,m)
10	2360	1701		*1.17(3H,t), 1.60-2.80(9H,m), 2.38(3H,s), 3.52(3H,s), 4.02(2H,q), 5.62(1H,s), 7.13-8.10(5H,m)
11	3470 3280	1670		1.07(3H,t), 0.80-3.27(9H,m), 2.30(3H,s), 3.57(3H,s), 3.99(2H,q), 6.08(1H,s), 6.90-7.80(5H,m)
12	2495	1699	1352	*0.77-2.57(11H,m), 2.42(3H,s), 3.62(3H,s), 3.70(3H,s), 5.30(1H,s), 7.26(1H,bs), 7.43-8.02(3H,m)
13	3200	1690	1350	2.30(3H,s), 3.52(3H,s), 3.60(5H,s), 5.00(1H,s), 6.73-8.23(4H,m)

14	3200	3110	1705	1347	**1.15(3H,t), 2.50(3H,s), 4.03(2H,q), 6.17(1H,bs), 6.45(1H,s), 7.10-8.17(9H,m), 10.33(1H,bs)
15	3360		1698	1345	**1.13(3H,t), 2.43(3H,t), 4.02(2H,q), 5.62(1H,s), 6.90(1H,bs), 7.13-8.03(9H,m)
16	3350		1665	1373	**2.42(3H,s), 3.50(3H,s), 3.80(3H,s), 5.52(1H,s), 7.03-7.93(14H,m), 9.57(1H,bs)
17	3280		1678	1350	1.18(3H,t), 2.43(3H,s), 3.77(3H,s), 4.07(2H,q), 5.50(1H,s), 6.78(1H,bs), 7.13-8.03(9H,m)
18	3313		1675	1375	2.32(3H,s), 3.35(3H,s), 3.80(3H,s), 6.05(1H,s), 7.07-7.77(9H,m), 9.60(1H,bs)
19	3340		1690	1346	1.20(3H,t), 2.45(3H,s), 3.80(3H,s), 4.10(2H,q), 5.50(1H,s), 6.55(1H,bs), 7.10-8.10(9H,m)
20	3355		1683	1350	2.40(3H,s), 3.53(3H,s), 3.83(3H,s), 5.47(1H,s), 7.20-8.00(8H,m), 9.60(1H,bs)
21	3350		1692	1350	1.25(3H,s), 2.43(3H,s), 3.80(3H,s), 4.12(2H,q), 5.48(1H,s), 7.03-8.10(7H,m)
22	3340		1692	1348	1.22(3H,t), 2.45(3H,s), 3.80(3H,s), 4.08(2H,q), 5.50(1H,s), 6.45(1H,bs), 7.17-8.02(7H,m)
23	3350		1692	1348	1.20(3H,t), 2.45(3H,s), 3.82(3H,s), 4.07(2H,q), 5.50(1H,s), 7.12(1H,bs), 7.18-8.05(8H,m)
24	3330		1723	1694 1343	1.22(3H,t), 2.43(3H,s), 3.80(3H,s), 3.93(3H,s), 4.09(2H,q), 5.60(1H,s), 7.18(1H,bs), 7.12-8.22(8H,m)
25	3270		1712	1668 1350	1.20(3H,t), 1.40(3H,t), 2.47(3H,s), 3.83(3H,s), 4.09(2H,q), 4.40(2H,q), 5.60(1H,s), 6.60(1H,bs), 7.07-8.23(8H,m)
26	3360		1695	1355	1.20(3H,t), 2.45(3H,s), 3.70(3H,s), 4.05(2H,q), 5.80(1H,s), 6.80(1H,bs), 7.00-8.70(8H,m)
27	3360		1701	1350	2.39(3H,s), 3.64(3H,s), 3.74(3H,s), 5.36(1H,s), 6.50-8.60(8H,m)

28	3320		1725	1700	1355	2.39(3H,s), 3.58(3H,s), 3.75(3H,s), 3.78(3H,s), 5.50(1H,s), 7.26-7.88(7H,m), 7.60(1H,bs)
29	3220	3120	1735	1693	1350	1.20(3H,t), 1.30(3H,t), 2.42(3H,s), 3.80(3H,s), 4.07(2H,q), 4.29(2H,q), 5.58(1H,s), 7.45(1H,bs), 7.18-8.15(4H,m)
30	3370		1725	1693	1350	1.20(3H,d), 1.32(3H,d), 2.38(3H,s), 3.63(3H,s), 3.78(3H,s), 5.17(1H,m), 5.58(1H,s), 7.35-8.02(4H,m), 8.07(1H,bs)
31	3290		1630		1350	1.18(3H,t), 2.43(3H,s), 3.77(6H,s), 4.07(2H,q), 5.50(1H,s), 6.67-8.07(9H,m)
32	3350		1695		1340	1.22-2.20(16H,m), 2.40(3H,s), 2.62(1H,m), 3.58(3H,s), 4.35(1H,m), 5.25(1H,s), 4.35(1H,bs), 7.30-8.13(4H,m)
33	3220		1690		1347	0.70, 0.84(6H,d), 1.82(3H,m), 2.40, 3.57, 3.67(9H,s), 5.20(1H,s), 7.08(1H,bs), 7.62(4H,m)
34	3300		1700		1350	1.08(9H,s), 2.42, 3.72, 3.78(9H,s), 5.45(1H,s), 6.57(1H,bs), 7.67(4H,m)
35	2560		1701		1347	0.53-1.62(9H,m), 2.22(2H,m), 2.37, 3.55, 3.63(9H,s), 5.20(1H,s), 7.12-8.20(4H,m) 2.73(1H,bs)
36	2640		1710		1350	0.33, 0.58(6H,d), 1.07, 2.34, 3.68, 3.73(12H,s), 1.49(4H,m), 5.32(1H,s) 7.13(1H,bs), 7.65(4H,m)
37	3225		1695		1350	0.27-1.67(5H,m), 2.40, 3.57, 3.60(9H,s), 5.28(1H,s), 7.02(1H,bs), 7.15-8.07(4H,m)
38	3320		1685		1360	0.70-2.87(11H,m), 2.37, 3.50, 3.67(9H,s), 5.87(1H,s), 7.12(1H,bs), 7.00-7.83(4H,m)
39	3355		1700		1350	1.07-2.62(13H,m), 2.40, 3.58, 3.67(9H,s), 5.25(1H,s), 6.97(1H,bs), 7.28-8.12(4H,m)
40	3340		1695		1340	0.70-2.35(10H,m), 0.84(3H,d), 2.41, 3.59, 3.68(9H,s), 5.27(1H,s), 6.79(1H,bs) 7.30-8.15(4H,m)

1	2600	1666	1344	0.33(3H,t), 0.73-2.53(12H,m), 2.36, 3.68, 3.73(9H,s), 5.30(1H,s), 6.88(1H,bs) 7.11-8.01(4H,m)
2		1667	1347	2.65, 3.18, 3.44, 3.60(12H,s), 5.38(1H,s), 6.82-7.88(6H,m), 8.65(1H,bs)

* Free base ** in DMSO-d6

Example 43

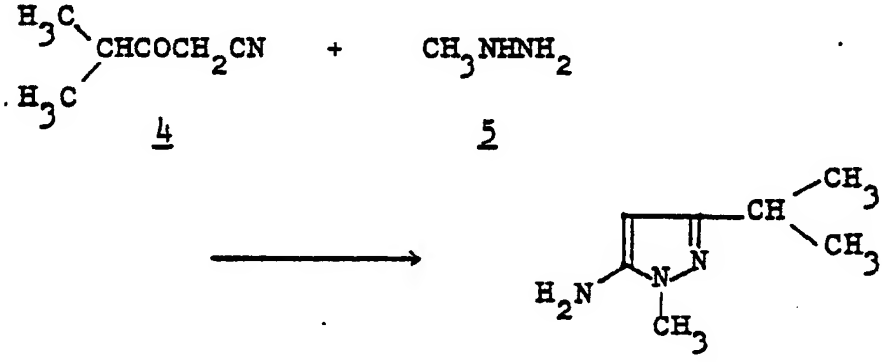
Component (Tablet)

Ethyl 3-cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate	10	mg
Corn starch	50	mg
Gelatin	7.5	mg
Avicel (microcrystalline cellulose)	25	mg
Magnesium stearate	2.5	mg
Total	95	mg

The above composition is formulated into one tablet.

Reference example 1

i) Preparation of 5-amino-3-isopropyl-1-methylpyrazole



4 5 6

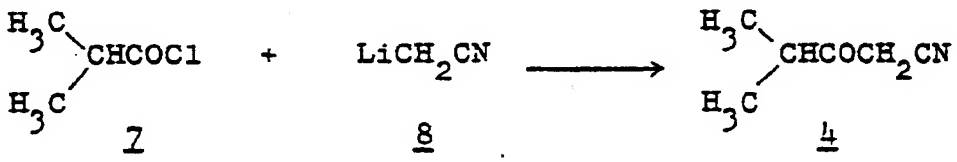
A mixture of 8.0 g (72 mmol) of 1-cyano-3-methyl-2-butanone 4 and 3.4 g (73.8 mmol) of methylhydrazine 5 in 2 ml of ethanol is stirred at room temperature for an hour, and concentrated under reduced pressure.

The resulting residue is chromatographed on silica gel. The chloroform fraction is recrystallized from carbon tetrachloride to give 8.48 g (84.6 % yield) of the titled compound as colorless prisms.

m.p. 111 - 112 °C

NMR: δ^{CDCl_3} 1.20 (6H, d), 2.60 - 3.10 (1H, m), 3.40 (2H, bs), 3.60 (3H, s), 5.30 (1H, s)

ii) Preparation of 1-cyano-3-methyl-2-butanone



7 8 4

To a solution (100 ml) of 0.2 mol of n-butyllithium in anhydrous tetrahydrofuran is dropwise added a solution of 8.2 g (0.2 mmol) of acetonitrile in 12 ml of tetrahydrofuran under nitrogen gas at - 70 °C within 30 minutes; after 2 hours, a solution of 10.65 g (0.1 mmol) of isobutyrylchloride in 18 ml of tetrahydrofuran is dropwise added thereto. After an hour, the reaction mixture is acidified with 10 % hydrochloric acid and extracted with ether, and the extract is washed with an aqueous sodium chloride solution, dried with magnesium sulfate, and evaporated. The residue is distilled to give 8.05 g (72.5 % yield) of the titled compound.

m.p. 62 - 65 °C

NMR: δ^{CDCl_3} 1.2 (6H, d), 2.6 - 3.1 (1H, m), 3.5 (2H, m)

Reference examples 2 - 19

In the same manner as in Refernce example 1, the compounds described in Table 8 can be prepared.

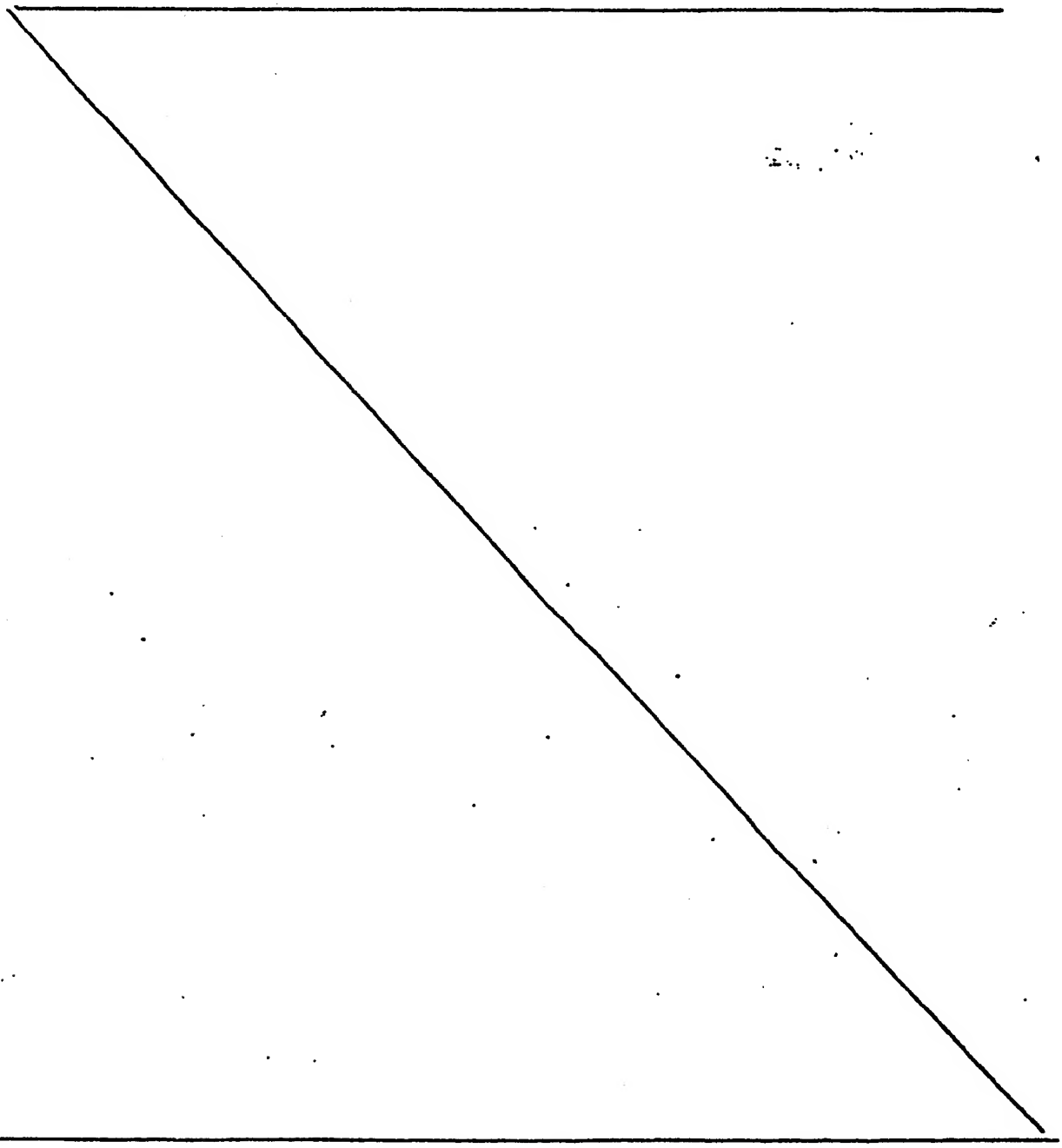
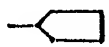
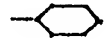
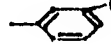
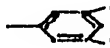
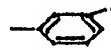
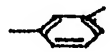
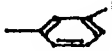
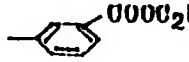
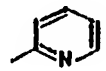
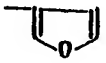
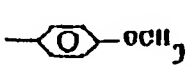


Table 8

Ref. Ex.	R^2	R^3	Yield (%)	M.P. (°C)	NMR (δ^{CDCl_3})
2	CH_3	$n\text{-}C_4H_9$	89.1		0.70-2.00(7H,m), 2.60(2H,t), 3.54(3H,s), 5.29(1H,s)
3	"		68.2	117-118	1.50-3.33(7H,m), 3.54(3H,s), 3.60(2H,bs), 5.38(1H,s)
4	"		74.4	149-150	1.33-2.20(8H,m), 2.60-3.10(1H,m), 3.57(3H,s), 5.32(1H,s)
5	"		71.7	173-174	0.90-2.77(11H,m), 3.43(2H,bs), 3.57(3H,s), 5.32(1H,s)
6	"		89.2	130-131	3.40(2H,bs), 3.53(3H,s), 3.78(2H,s), 5.22(1H,s), 7.23(5H,s)
7	H		94.3	110-111	4.75(2H,bs), 5.80(1H,s), 7.10-7.77(5H,m)
8		"	78.0	130-131	5.83(1H,s), 7.20-7.80(5H,m)
9	CH_3	"	92.4	130-131	3.58(3H,s), 3.50(2H,bs), 5.73(1H,s), 7.15-7.78(5H,m)
10	"		91.0	127-128	3.65(3H,s), 5.80(1H,s), 7.10-7.80(4H,m)
11	"		99.1	155-156	3.63(3H,s), 3.63(2H,bs), 5.72(1H,s), 7.07-7.67(3H,m)
12	"		62.2	91-92	3.58(2H,bs), 3.68(3H,s), 5.85(1H,s), 7.30-8.07(4H,m)
13	"		79.1	179-181	3.55(2H,bs), 3.69(3H,s), 5.81(1H,s), 7.48-7.85(4H,m)
14	"		76.8	101-102	3.63(2H,bs), 3.68(3H,s), 3.90(3H,s), 5.88(1H,s), 7.42-8.37(4H,m)

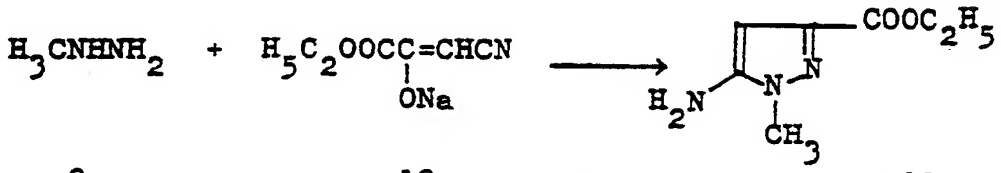
15	CH_3		77.9	113-114	1.38(3H,t), 3.62(2H,bs), 3.68(3H,s), 4.38(2H,q), 5.88(1H), 7.40-8.36(4H,m)
16	"		53.5	186-187	3.65(2H,bs), 3.70(3H,s), 6.15(1H,s), 7.00-8.00(4H,m)
17	"		14.2	118-120	3.52(2H,bs), 3.65(3H,s), 5.63(1H,s), 6.68-7.69(3H,m)
18	"		75.1	140-141	3.65(3H,s), 3.78(3H,s), 5.75(1H,s), 6.73-7.67(4H,m)
19			71.5	92-93	1.2-2.33(16H,m), 2.97(1H,m), 3.42(2H,bs), 4.35(1H,m), 5.33(1H,s)

-35-

0107619

Reference example 20

Preparation of ethyl 5-amino-1-methylpyrazole-3-carboxylate



9 10 11

A mixture of 10 g (61.3 mmol) of the sodium salt of ethyl 3-cyanopyruvate 10 and 9.0 g (61.3 mmol) of methylhydrazine sulfate 9 in 100 ml of methanol is stirred at room temperature for 3 days, and then concentrated under reduced pressure. To the resulting residue are added an aqueous sodium bicarbonate solution and an aqueous sodium chloride solution, and the mixture is extracted 6 times with chloroform, dried with magnesium sulfate, and chromatographed on a column of silica gel. The ethyl acetate eluate gives 6.54 g (62.9 % yield) of the titled compound 11 as an yellow oil.

NMR: δ^{CDCl_3} 1.35 (3H, t), 3.71 (3H, s), 3.76 (2H, bs), 4.35 (2H, q), 6.03 (1H, s)

Reference example 21

Preparation of methyl 5-amino-1-methylpyrazole-3-carboxylate

To a solution of 48 mg (2.1 mmol) of sodium in 40 ml of methanol is added 2.0 mg (11.8 mmol) of 5-amino-3-ethoxy-

carbonyl-1-methylpyrazole, and the mixture is refluxed over night, and distilled under reduced pressure. To the resulting residue are added a small amount of water and sodium chloride, and the mixture is extracted 6 times with chloroform. The extract is dried with magnesium sulfate, chromatographed on a column of silica gel and eluted with ethyl acetate to give 1.37 g (74.1 % yield) of the titled compound.

m.p. 101 - 102 °C

NMR: δ^{CDCl_3} 3.71 (3H, s), 3.86 (3H, s), 3.90 (2H, bs), 6.05 (1H, s)

Reference example 22

Preparation of isopropyl 5-amino-1-methylpyrazole-3-carboxylate

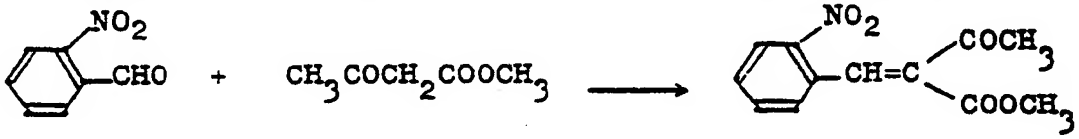
In the same manner as in Reference example 19. the titled compound can be prepared. (Yield: 72.9 %)

m.p. 86 - 87 °C

NMR: δ^{CDCl_3} 1.37 (6H, d), 3.72 (3H, s), 3.75 (2H, bs), 5.23 (1H, m)

Reference example 23

Preparation of methyl 2-nitrobenzylidene acetate



12 13 14

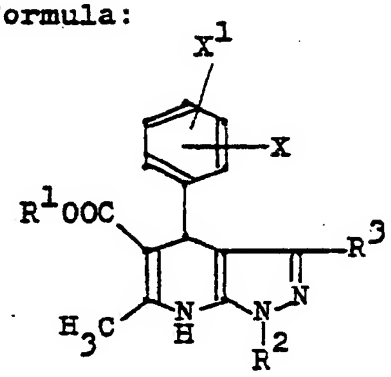
To 40 ml of benzene are added 11.6 g (0.1 mol) of methyl acetoacetate 13, 15 g (0.1 mol) of 2-nitrobenzaldehyde 12, 3 ml of acetic acid, and 0.8 ml of piperidine, and the mixture is kept at room temperature for 3 days, after which is added 12 g (0.1 mol) of magnesium sulfate thereto. The reaction mixture is stirred for 4 days, and filtered. Benzene is distilled off, and the residue is recrystallized from ethanol to give 22.5 g (90.0 % yield) of the titled compound 14 as colorless prisms.

m.p. 100 - 101 °C

NMR: δ^{CDCl_3} 2.47 (3H, s), 3.60 (3H, s), 7.23 - 8.37 (4H, m)

Claims

1. Dihydropyrazolo[3,4-b]pyridine derivatives represented by the general formula:



[wherein X and X^1 each is hydrogen, nitro, or halogen which may be located at the position or positions 2, 3, and/or 6;

R^1 is C_1- C_4 alkyl;

R^2 is hydrogen, C_1- C_4 alkyl, C_4- C_6 cycloalkyl, or phenyl;

R^3 is hydrogen, C_1- C_8 straight or branched chain alkyl, or C_3- C_7 cycloalkyl which may be substituted by C_1- C_3 alkyl, substituted or unsubstituted phenyl, C_7- C_9 aralkyl, C_1- C_4 alkoxycarbonyl, or 5- or 6- membered heterocyclic group containing an oxygen or nitrogen]

and their acid addition salts.

2. A compound claimed in claim 1, wherein X is nitro; X^1 is hydrogen; R^1 is C_1- C_4 alkyl; R^2 is C_1- C_4 alkyl; R^3 is C_1- C_8 straight or branched chain alkyl, or C_3- C_7 cycloalkyl.

3. A compound claimed in claim 1, namely, methyl 3-(n-butyl)-

1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]-pyridine-5-carboxylate.

4. A compound claimed in claim 1, namely, methyl 3-(i-butyl)-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo[3,4-b]-pyridine-5-carboxylate.

5. A compound claimed in claim 1, namely, methyl 3-cyclobutyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo-[3,4-b]pyridine-5-carboxylate.

6. A compound claimed in claim 1, namely, methyl 3-cyclopentyl-1,6-dimethyl-4-(2-nitrophenyl)-4,7-dihydropyrazolo-[3,4-b]pyridine-5-carboxylate.

7. A compound claimed in claim 1, namely, methyl 3-cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo-[3,4-b]pyridine-5-carboxylate.

8. A compound claimed in claim 1, namely, ethyl 3-cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo-[3,4-b]pyridine-5-carboxylate.

9. A compound claimed in claim 1, namely, isopropyl 3-cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo-[3,4-b]pyridine-5-carboxylate.

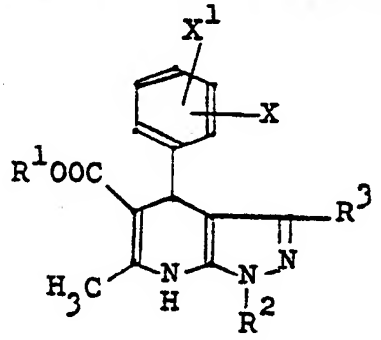
10. A compound claimed in claim 1, namely, methyl 3-cyclohexyl-1,6-dimethyl-4-(2-nitrophenyl)-4,7-dihydropyrazolo-[3,4-b]pyridine-5-carboxylate.

11. A compound claimed in claim 1, namely, methyl 3-cyclohexyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo-

[3,4-b]pyridine-5-carboxylate.

12. A compound claimed in claim 1, namely, methyl 3-cycloheptyl-1,6-dimethyl-4-(3-nitrophenyl)-4,7-dihydropyrazolo-[3,4-b]pyridine-5-carboxylate.

13. A process for producing dihydropyrazolo[3,4-b]pyridine derivatives represented by the general formula:



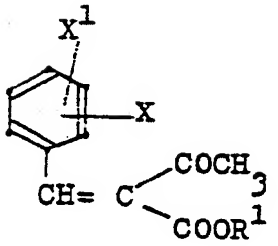
[wherein X and X^1 each is hydrogen, nitro, or halogen which may be located at the position or positions 2, 3, and/or 6;

R^1 is C_1- C_4 alkyl;

R^2 is hydrogen, C_1- C_4 alkyl, C_4- C_6 cycloalkyl, or phenyl;

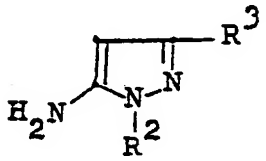
R^3 is hydrogen, C_1- C_8 straight or branched chain alkyl, or C_3- C_7 cycloalkyl which may be substituted by C_1- C_3 alkyl, substituted or unsubstituted phenyl, C_7- C_9 aralkyl, C_1- C_4 alkyloxycarbonyl, or 5- or 6- membered heterocyclic group containing an oxygen or nitrogen]

which comprises reacting a compound represented by the general formula:



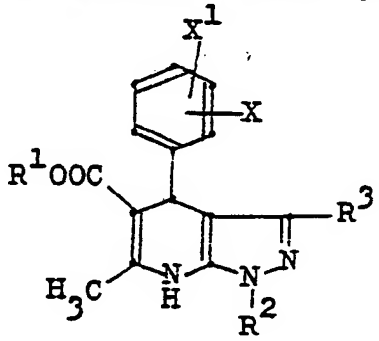
[wherein X, X^1, and R^1 each has the same significance as defined above]

with a compound represented by the general formula:



[wherein R^2 and R^3 each has the same significance as defined above].

14. Medicinal compositions comprising one or more members selected from the group consisting of dihydropyrazolo[3,4-b]-pyridine derivatives represented by the general formula:



[wherein X and X^1 each is hydrogen, nitro, or halogen which may be located at the position or positions 2, 3, and/ or 6;

R^1 is C_1- C_4 alkyl;

R^2 is hydrogen, C_1- C_4 alkyl, C_4- C_6 cycloalkyl, or phenyl;

R^3 is hydrogen, C_1- C_8 straight or branched chain alkyl, or C_3- C_7 cycloalkyl which may be substituted by C_1- C_3 alkyl, substituted or unsubstituted phenyl, C_7- C_9 aralkyl, C_1- C_4 alkyloxycarbonyl, or 5- or 6- membered heterocyclic group containing an oxygen or nitrogen]

and their pharmaceutical acceptable acid addition salts and pharmaceutical carriers.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 83 81 0442

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
A	US-A-3 857 849 (BAYER) * Column 1, lines 6-48 * -----	1,14	C 07 D 471/04 A 61 K 31/435// C 07 D 231/38 C 07 D 401/04 C 07 D 407/04 (C 07 D 471/04 C 07 D 231/00 C 07 D 221/00)

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

C 07 D 471/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11-01-1984	ALFARO I.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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